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Reactions with pyrrolidine-2,4-diones, part 4*: Synthesis of some 3-substituted 1,5-diphenylpyrrolidine-2,4-diones as potential antimicrobial, anti-HIV-1 and antineoplastic agents

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The condensation of 1,5-diphenylpyrrolidine-2,4-dione (**1**) with ethyl orthoformate yielded 3-ethoxymethylene-1,5-diphenylpyrrolidine-2,4-dione (**2**). Reaction of the latter with hydrazine hydrate, secondary amines **7a–c** or urea afforded the corresponding 3-substituted aminomethylene-1,5-diphenylpyrrolidene-2,4-diones **3, 8a–c or 9**. On the other hand, condensation of **3** with veratraldehyde (**5a**) yielded 3-[(3,4-dimethoxybenzylidene)hydrazinomethylene]-1,5-diphenylpyrrolidine-2,4-dione (**6**). Whereas, cyclization of **9** with the reactive malonate ester **11** produced 3-[(5-butyl-4-hydroxy-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-1-yl) methylene]-1,5-diphenylpyrrolidine-2,4-dione (**12**). The condensation of some selected aromatic aldehydes **5a–c** and addition of morpholine (**7c**) or piperidine (**7d**) to some of the resulting 3-arylidene-1,5-diphenylpyrrolidine-2,4-diones **13b**, **c** gave the respective 3-substituted methyl-4-hydroxy-1,5-diphenyl-Δ^3-pyrrolin-2-ones **14a–c**. Selected members of the new series were screened for their *in vitro* antimicrobial, anti-HIV-1 and antineoplastic activities. Two compounds **14a**, **b** showed pronounced inhibitory activities against Gram-positive bacteria; whereas, in the *in vitro* anti-HIV-1 screening, only one compound **13c** displayed a moderate activity. However, in the antineoplastic screening protocol, the tested compounds were devoid of activity.

1. Introduction

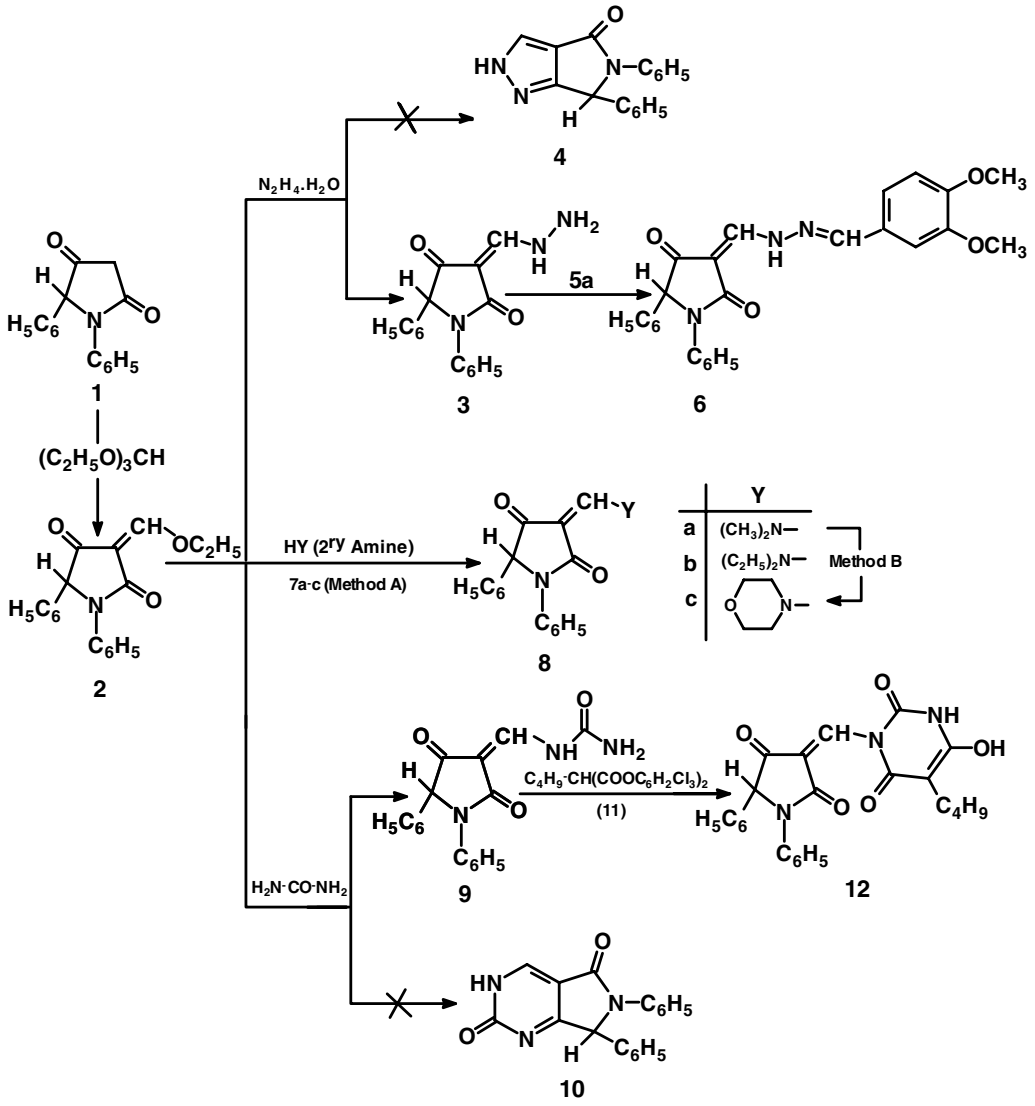
A literature survey indicated that a number of microbial derived metabolites which possess 3-acylpyrrolidine-2,4-dione skeleton demonstrated variable degrees of activities against certain types of microbes, viruses or cancer cells [2–16]. The natural products vary in structural complexity from simple tenuazonic acid [2, 3] and magnesidin [12] to the more elaborate streptolydigin [4] and tirandamycin A and B [4]. Additionally, a number of synthetic pyrrolidine-2,4-diones proved to be antimicrobial and few showed anticancer and antiviral activities [17–19]. On bases of these reports and for further development of the previous work from this laboratory [1], the synthesis of new pyrrolidine-2,4-diones with potential antimicrobial, anti-HIV and anticancer activities was projected. The structural modification of position 3 of 1,5-diphenylpyrrolidine-2,4-dione (**1**) previously reported from this laboratory [20], was considered an interesting approach that would help to assist the structural features necessary for each of the desired biological properties. The 3-substituted aminomethylene derivatives **3, 8a–c,** and **9** (Scheme 1) seemed attractive in respect to the predicted activity since some substituted 3-(anilinoethylidene)pyrrolidine-2,4-diones proved to have potent antineoplastic activity [19]. Conversion of **1** to 3-arylidene-1,5-diphenylpyrrolidine-2,4-diones **13a–c** was also projected (Scheme 2). This series was looked upon as having an olefinic group conjugated to C_4=O. This structural feature was reported to be an important pharmacophore among some antimicrobial and antineoplastic agents whose bioactivities were attributed to the ability of the conjugated system to alkylate biologically important nucleophiles. Encouraged by the *in vitro* activity of 4-hydroxy-3-(isopropyl- and isobutyl-aminomethyl)-1,5-diphenyl-Δ^3-pyrrolin-2-one against Gram-positive bacteria [1], further modification of the 3-amino side chain was thought off. In this respect, compounds **14a–c** were proposed where the oxygen function at position 4 of the ring system would occur predominantly as enolic OH.

2. Investigations and results

2.1. Synthesis of compounds

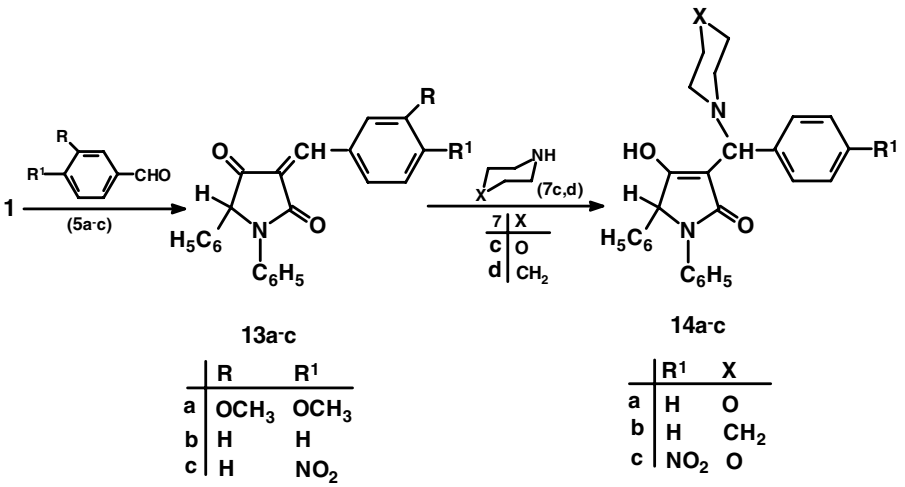
The desired compounds were synthesized by the reactions outlined in Schemes 1 and 2. Reaction of 1,5-diphenylpyrrolidine-2,4-dione (**1**) with ethyl orthoformate yielded the key intermediate, 3-ethoxymethylene-1,5-diphenylpyrrolidine-2,4-dione (**2**). In the MS, this compound did not show the molecular ion peak but revealed a peak at m/z 279, which corresponds to $M^+ - C_2H_4$ ion. The condensation of **2** with hydrazine hydrate would hypothetically lead to the desired pyrazolylpyrrole derivative **4** via an intermediate enhydrazine. However, when the reaction was performed in warm ethanol, only the enhydrazine **3** was isolated in an excellent yield. Its IR revealed two CO absorption bands. Condensation of the hydrazino derivative **3** with veratraldehyde (**5a**) to yield the corresponding benzylidene derivative **6** confirmed the presence of a free primary amino group. The 3-substituted aminomethylenes **8a–c** were prepared by condensing **2** with different secondary amines **7a–c** (method A). Their IR showed two carbonyl absorption bands. In this series, compound **8c** could also be obtained in a high yield from 3-dimethylaminomethylene-1,5-diphenylpyrrolidine-2,4-dione (**8a**) and morpholine (**7c**) (method B) where the dimethylamino moiety was displaced by morpholine. Reaction of 3-ethoxymethylene-1,5-diphenylpyrrolidine-2,4-dione (**2**) with an equimolar quantity of urea in ethanol afforded a single product. Its elemental analysis, IR and ^{1}H NMR data coincided with structure **9**, 1,5-diphenyl-3-ureidomethylenepyrrolidine-2,4-dione, excluding the probability of formation of fused pyrimidinopyrrole **10**. Fusing compound **9** with bis (2,4,6-trichlorophenyl)butyl malonate (**11**) yielded 3-[(5-butyl-4-hydroxy-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-1-yl)methylene]-1,5-diphenylpyrrolidine-2,4-dione (**12**). Condensation of **1** with the appropriate aldehyde **5a–c** in acidic medium produced the respective 3-arylidene-1,5-diphenylpyrrolidine-2,4-diones **13a–c.** Compound **13b** has been described ealier [20]. 3-Disubstituted methyl-4-hydroxy-1,5-diphenyl-Δ^3-pyrroline-2-ones **14a–c** were pre-

Scheme 1



pared in good yields by reacting **13b** or **13c** with either morpholine (**7c**) or piperidine (**7d**) in ethanol. Two tautomeric forms of compounds **14a–c** are theoretically possible. IR spectral data revealed the OH and the α,β-unsaturated C_2=O absorptions corresponding to the enolic structure. ^{1}H NMR spectra of **14a** and **14c** were also consistent with the enolic structure since they lacked a C_3-H signal. Spectrum of **14a** also showed the OH as broad signal at δ

Scheme 2



8.5–9 ppm. By contrast, compound **13a** failed to react with the selected secondary amines **7c** and **7d**. This could indicate that the presence of electron releasing methoxy groups inhibited the nucleophilic attack of the amine at the 1,4 positions.

2.2. Preliminary antimicrobial screening

Compounds **1**, **2, 3, 8a–c**, **9**, **13a**, **c** and **14a–c** were screened for their *in vitro* activities against three clinically isolated *S. aureus* strains (Oxford strain, penicillinase-producing strain and methicillin-resistant strain) as Gram-positive bacteria, two Gram-negative bacilli (one strain of *E. coli* and one strain of *P. aeruginosa*) and one *C. albicans* strains as a fungus. The agar diffusion method in tryptic soy agar was adopted to determine the growth inhibition zones [21]. Compounds that showed acceptable values of inhibition zone diameters ($\geq$17 mm) at the adopted concentration level (20 µl of 10mg/ml dimethylformamide) were evaluated for their inhibitory concentration (MIC) in µg/ml against the most sensitive organism, using two-fold serial dilution technique [21]. Amikacin was used as reference drug and a control experiment without the test was included for each organism. Out of the compounds tested, **14a** and **b** showed considerable growth inhibition effects against the *S. aureus* strains used. However, none of the tested compounds were inhibitory for the test Gram-negative bacilli and *C. albicans* fungus (Table 1). It is note-worthy that data recorded for Mannich bases **14a** and **b** are in accordance with those previously reported from this laboratory for related derivatives [1].

2.3. In vitro Anti-HIV-1 screening

Seven compounds **3**, **8b**, **c**, **13a**, **c** and **14a**, **c** were screened for their *in vitro* anti-HIV-1 activity following the National Cancer Institute *in vitro* anti-HIV screening protocol [22]. The procedure used was designed to detect agents acting at any stage of the virus reproductive cycle. The assay basically involved killing of T_4 Lymphocytes by HIV. Small amounts of HIV were added to cells, and a complete cycle of virus reproduction was necessary to obtain the required cell killing. Agents that interact with virions, cells, or virus gene-products to interfere with viral activities would protect cells from cytolysis. However, compounds that degenerated or rapidly metabolized in the culture condition might not show activity in this screen. All tests were compared with at least one positive control done at the same time under identical conditions (e.g. AZT treated). Among the tested compounds, compound **13c** revealed moderate activity, showing a survival value of 93.69 at a therapeutic index $> 7.2 \times 10$ and molar concentration of 2×10^{-5}. Although compounds **3**, **8b**, **14a** and **14c** were considered inactive in this screen, it was noted that they gave survival values of 37.05, 41.94, 47.74 and 57.62 at molar concentrations of 2×10^{-10}, 2×10^{-10}, 2×10^{-5}, and 1×10^{-6}, respectively.

2.4. Antineoplastic evaluation

Compounds **3**, **8b**, **c**, **13a**, **c** and **14a**, **c** were screened for their *in vitro* antineoplastic activity following the National Cancer Institute *in vitro* disease oriented primary screening program [23]. In this program, each compound was tested over a broad concentration range against a total of 56 human cell lines derived from eight cancer types. None of the tested compounds reached the statistically significant values of the different response parameters.

3. Experimental

Melting points were determined in open-glass capillaries and are uncorrected. The IR spectra were recorded for KBr discs, using a Perkin-Elmer 421 spectrophotometer. The ^{1}H NMR spectra were recorded on a Varian EM-360 or Joel Fx 90a 90 MHz NMR spectrometer using DMSO-D_6 as solvent and TMS as internal standard. The MS spectra were determined with GC-MS 1000 Fx Shimadzu mass spectrometer. An inlet temperature of 250 °C and electron beam of 70 ev were used. Microanalysis, for samples dried over $CaCl_2$ at room temperature under reduced pressure, were performed at the Microanalytical Unit, Faculty of Science, University of Cairo, A.R. Egypt, at the Institute of Organic Chemistry, University of Graz, Austria or at the Pharmazeutisches Institut, Freiburg, Germany. Light petroleum had b.p. 60–80 °C. Anti-HIV and anti-cancer screening were conducted by the National Cancer Institute, Bethesda, M.D., USA.

3.1. 3-Ethoxymethylene-1,5-diphenylpyrrolidine-2,4-dione (**2**)

Compound **1** [20] (1 g, 4 mmol) was warmed with ethyl orthoformate (3.3 ml, 20 mmol) until the solid was dissolved giving a dark reddish solution. After cooling, ether was added and the orange precipitate was filtered, washed with ether and dried. It was crystallized from benzene-light petroleum as orange crystals, m.p. 150–151 °C; yield 0.8 g (65%). IR: 3027, 2983, 2903 (triplet of aromatic O–C_2H_5); a band splitted at 1723 (C_4=O), 1667 (C_2=O) and at 1613 (C=C and aromatics); 1260 (=C–O–C; asym. streching); 1098 cm^{-1} (=C–O–C, sym. strechning). ^{1}H NMR: δ 1.0 (t, J = 7.5 Hz, 3 H, CH_3); 3.37 (q, J = 7.5 Hz, 2 H, CH_2); 5.48 (s, 1 H, C_5–H); 6.75–7.56 (m, 10 H, Ar-H); 8.1 (s, 1 H, =CH–). MS: m/z (relative abundance%) 279 (7, $M^+-C_2H_4$); 244 (9); 242 (9); 197 (8); 171 (24), 169 (23); 165 (9); 164 (77); 163 (29); 150 (9); 149 (10); 136 (14); 135 (94); 105 (19); 93 (66); 92 (14); 91 (100, $C_7H_7^+$); 76 (25); 75 (45); 61 (43); 60 (25).
$C_{19}H_{17}NO_3$ (307.4)

3.2. 3-Hydrazinomethylene-1,5-diphenylpyrrolidine-2,4-dione (**3**)

Hydrazine hydrate (0.1 ml, 2 mmol) was added to a solution of compound **2** (0.6 g, 2 mmol) in C_2H_5OH (10 ml) and the mixture was warmed for 5 min. After cooling, the yellow product was filtered, dried and crystallized from benzene, m.p. 243–245 °C; yield 0.5g (85.2%). IR : 3310, 3200 (NH, NH_2); a band splitted at 1681 (C_4=O); 1637 (C_2=O) and at 1591 (C=C and aromatics). ^{1}H NMR: δ 5.4 (s, 1 H, C_5–H); 6.7–7.6 (m, 10 H, Ar-H); 7.65 (s, 1 H, =CH–).
$C_{17}H_{15}N_3O_2$ (293.3)

3.3. [(3,4-Dimethoxybenzylidene)hydrazinomethylene]-1,5-diphenylpyrrolidine-2,4-dione (**6**)

A solution of **3** (0.3 g, 1 mmol) and **5a** (0.17 g, 1 mmol) in HOAc (5 ml) was refluxed for 1 h. After cooling, the product was filtered, dried and crystallized from HOAc as yellow crystals, m.p. 139–140 °C; yield 0.3 g (68%). IR: 3654–3000 (NH, CH, CH_3), a band splitted at 1689 (C_4=O), 1642 (C_2=O) and at 1615 cm^{-1} (C=C and aromatics). ^{1}H NMR: δ 3.74 (s, 6 H, two OCH_3); 5.55 (s, 1 H, C_5–H); 6.85–7.71 (m, 13 H, Ar-H); 7.85 (s, 1 H, =CH); 8.41 (s, 1 H, NH).
$C_{26}H_{23}H_4O_4$ (441.5)

Table 1: Inhibition zone diameters in mm of the active compounds and their minimal inhibitory concentrations (MIC) in µg/ml

Compd.	*S. aureus*			*E. coli*	*P. aeruginosa*	*C. albicans*
	Oxford	Penicillinase producing	Methicillin			
14a	19 (20)	20 (50)	19 (50)	–	–	–
14b	21 (20)	21 (20)	19 (50)	–	–	–
Amikacin	$\geq$17 (1)	$\geq$17 (1)	$\geq$17 (1)			

3.4. 3-Substituted aminomethylene-1,5-diphenylpyrrolidine-2,4-diones 8a–c

3.4.1. Method A

To a well stirred solution of **2** (0.6 g, 2 mmol) in benzene (10 ml) was added, dropwise, a solution of the appropriate secondary amine **7a–c** (2 mmol) in benzene (5 ml) and few drops of C_2H_5OH under ambient conditions. Stirring was continued for further 30 min, then the reaction mixture was left to stand for overnight. The precipitate was filtered, washed with cold benzene, dried and crystallized from the suitable solvent. IR data are included in Table 2.

3.4.2. Method B for 8c

The compound was prepared from **8a** (0.6 g, 2 mmol) and morpholine (**7c**) (0.17 ml, 2 mmol) following the procedure described under method A, using $C_6H_5-C_2H_5OH$ mixture (1 : 1) (10 ml) as solvent, m.p. 234–235 °C; yield 0.6 g (85.7%).^{1}H NMR of compound **8a**: δ 3.6 (s, 6 H, $N(CH_3)_2$, 5.4 (s, 1 H, C_5-H); 6.8–7.6 (m, 10 H, Ar-H and 1 H, =CH–). ^{1}H NMR of compound **8c**: δ 3.5–4.46 (2m, 8 H, CH_2-O-CH_2 and CH_2-N-CH_2); 5.54 (s, 1 H, C_5-H); 6.9–7.7 (m, 10 H, Ar-H and 1 H, =CH–). MS of compound **8b**: m/z (relative abundance%) 334 (M^+, 100, $C_{21}H_{22}N_2O_2$), 305 (9); 240 (6).

3.5. 1,5-Diphenyl-3-uridomethylenepyrrolidine-2,4-dione (9)

A solution of compound **2** (0.6 g, 2 mmol) in C_2H_5OH (10 ml) was treated with a solution of urea (0.12 g, 2 mmol) in C_2H_5OH (5 ml) and the mixture was refluxed for 1 h. After cooling, the precipitate was filtered, dried and crystallized from C_2H_5OH as yellow crystals, m.p. 214–215 °C; yield 0.4 g (62.2%). IR: a band splitted at 3361 and 3192 (NH, NH_2, =CH–); 1706 (C_4=O); 1659 (C=O urea-amide I band); 1628 (C_2=O); 1583 cm^{-1} (C=C, aromatics and urea-amide II band).
$C_{18}H_{15}N_3O_3$ (321.3)

3.6. 3-[(5-Butyl-4-hydroxy-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-1-yl) methylene]-1,5-diphenylpyrrolidine-2,4-dione (12)

A mixture of **9** (0.3 g, 1 mmol) and bis (2,4,6-trichloropheny)butylmalonate (**11**) [24] (0.5 g, 1 mmol) was heated at 200 °C in an oil bath for 10 min. After cooling, the solid brownish mass was crystallized from $C_2H_5OH-C_2H_5-O-C_2H_5$ as yellow crystals, m.p. 260 °C; yield 0.15 g (33.7%). IR: 3635–3000 (NH, OH); 3000–2629 (=CH, CH_2, CH_3); a band plitted at 1712, 1670 and 1617 (C=O); 1594 and 1494 cm^{-1} (C=C and aromatics).
$C_{25}H_{23}N_2O_5$ (445.5)

3.7. 3-Arylidene-1,5-diphenylpyrrolidine-2,4-dione 13a–c

General procedure: A solution of **1** (0.5 g, 1 mmol) and the appropriate aldehyde **5a–c** (2 mmol) in C_2H_5OH (10 ml) was treated with either 2 drops of concentrated H_2SO_4 in the case of compounds **13a** and **13b** [20] or 2 drops of concentrated HCl in the case of compound **13c**. The mixture was warmed for 5 min then left at room temperature for overnight. The resulting yellow precipitate was filtered, washed with cold C_2H_5OH, dried and crystallized from C_6H_6.

3.7.1. 3-(3,4-Dimethoxybenzylidene)-1,5-diphenylpyrrolidine-2,4-dione (13a)

M.p. 149–150 °C; yield 69%. IR: 2960, 2940, 2900 (triplet of aromatic OCH_3); 1720 (C_4=O); 1670 (C_2=O); 1565 (C=C and aromatics); 1280 (=C–O–C asym. streching), 1110 cm^{-1} (=C–O–C sym. streching). ^{1}H NMR: δ 3.85 (s, 6 H, two OCH_3); 5.40 (s, 1 H, C_5-H); 6.78–7.85 (m, 13 H, Ar-H); 8.0 (s, 1 H, =CH). MS: m/z (relative abandance%) 399 (M^+, 100); 295 (25); 190 (83); 18 (67); 181 (60); 180 (73); 152 (10); 77 (37).
$C_{25}H_{21}NO_4$ (339.5)

3.7.2. 3-(4-Nitrobenzylidene)-1,5-diphenylpyrrolidine-2,4-dione (13c)

M.p. 139–140 °C; yield 42.1%. IR: a strong band splitted at 1630 and at 1590 with shoulders at 1700, 1660 and 1640 (C_4=O, C_2=O, C=C and aromatics); 1500 cm^{-1} (C-NO_2, asym. streching). ^{1}H NMR: δ 5.53 (s, 1 H, C5-H); 7.07–8.80 (m, 14 H, Ar-H and 1 H, =CH).
$C_{23}H_{16}N_2O_4$ (384.4)

3.8. 3-Disubstituted methyl-4-hydroxy-1,5-diphenyl-Δ^3-pyrrolin-2-ones 14a–c

General procedure: Morpholine (**7c**) or piperidine (**7d**) (2 mmol) was added to a stirred suspension of the appropriate 3-arylidene-1,5-diphenylpyrrolidine-2,4-dione **13b**,**c** (2 mmol) in C_2H_5OH (10 ml) and then warmed to effect dissolution. Stirring was continued at room temperature for 1 h and the product, which separated out, was filtered, dried and crystallized from the proper solvent. IR data are recorded in Table 3. ^{1}H NMR of compound **14a**: δ 3.15 (t, J = 2.4 Hz, 4 H, CH_2-N-CH_2); 3.75 (t, J = 2.4 Hz, 4 H, CH_2-O-CH_2); 5.07 (s, 1 H, CH–N); 5.35 (s, 1 H, C_5-H); 6.58–7.69 (m, 15 H, Ar-H); 8.5–9 (br, 1 H, OH). ^{1}H NMR of compound **14c**: δ 3.05 (t, J = 4.5 Hz, 4 H, CH_2-N-CH_2); 3.75 (t, J = 4.5 Hz, 4H, CH_2-O-CH_2); 5.1 (s, 1H, CH–N); 5.35 (s, 1 H, C_5-H); 6.6–8 (m, 14 H, Ar-H).

[*] For part 3 see [1].

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References

1 Shams EL-Dine, S. A.; Kassem, M. G.; Soliman, F. S. G. Saudi, M. N. S.; Kader, O.: Farmaco **46**, 1179 (1991)
2 Sticklings, C. E: Biochem. J. **72**, 332 (1959)
3 Poncet, J; Jouin, P.; Castro, B.; Nicolas, L.; Boutar, M.; Gaudemer, A.: J. Chem. Soc. Perkin Trans. 1, 611 (1990)

Table 2: 3-Substituted aminomethylene-1,5-diphenylpyrrolidine-2,4-diones 8a–c

Compd.	Y	Yield (%)	Melting point (°C) (cryst. solvent)	Molecular Formula (Molecular weight)	IR (cm^{-1})
8a	$-N(CH_3)_2$	83.3	245–246 ($C_6H_6-C_2H_5OH$)	$C_{19}H_{18}N_2O_2$ (306.4)	3656–2750 (=CH, CH_3); a band splitted at 1692 (C_4=O), 1638 (C_2=O) and at 1612 (C=C and aromatics)
8b	$-N(C_2H_5)_2$	66	172–173 (C_6H_6)	$C_{21}H_{22}N_2O_2$ (334.4)	3100–2600 (=CH, CH_2, CH_3), a band splitted at 1700 (C_4=O), and at 1640 (C_2=O) and at 1600 (C=C and aromatics).
8c	C_4H_8NO	87	235 (C_2H_5OH)	$C_{21}H_{20}N_2O_3$ (348.4)	3100–2800 (–CH, CH_2); 1690 (C_4=O); 1640 (C_2=O); 1590 (C=C and aromatics)

Table 3: 3-Disubstituted methyl-4-hydroxy-1,5-diphenyl-Δ^3-pyrrolin-2-ones 14a–c

Compd.	R^1	X	Yield (%)	Melting point (°C) (cryst. solvent)	Molecular Formula (Molecular weight)	IR (cm^{-1})
14a	H	O	50	184–185 C_2H_5OH	$C_{27}H_{26}N_2O_3$ (426.5)	3598–3057 (OH); 3057–2691 (CH, CH_2) 1646 (C_2=O); 1593 (C=C and aromatics)
14b	H	CH_2	64.5	210–212 $C_2H_5OH-H_2O$	$C_{28}H_{28}N_2O_2$ (424.6)	3694–3059 (OH); 3059–2661 (CH, CH_2); 1613 (C_2=O); 1494 (C=C and aromatics).
14c	NO_2	O	83.3	178–180 C_2H_5OH/H_2O	$C_{27}H_{25}N_3O_5$ (471.5)	3717–3056 (OH); 3056–2630 (CH, CH_2); 1629 (C_2=O); 1593 (C=C and aromatics)

4 Shimshock, S. J.; Waltermire, R. E.; De Shong, P.: J. Am. Chem. Soc. **113**, 8791 (1991)
5 Jones, R. C. F.; Tankard, M.: J. Chem. Soc. Perkin Trans. 1 240 (1991)
6 Holzapfel, C. W.: Tetrahedron **24**, 2101 (1968)
7 Holzapfel C. W.; Hutchison, R. D.; Wilkins, D. C.; Tetrahedron **26**, 5239 (1970)
8 Jones, R. C. F.; Begley, M. J.; Peterson, G. E.; Sumaria, S.: J. Chem. Soc. Perkin Trans. 1 1959 (1990)
9 Batelaan, J. G.; Barnick, J. W. F. K.; Van der Baan, J. L.; Bickelhaupt, F.: Tetrahedron Lett. 3107 (1972)
10 Schabacher, K.; Zeeck, A.: Tetrahedron Lett. 2691 (1973)
11 Horváth, Gy.; Gyimesi, J.; Méheshfalvi-Vajana, Zs.;: Tetrahedron Lett. 3643 (1973)
12 Kohl, H.; Bhat, S. V.; Patell, J. R.; Ghandi, N. M.; Nazareth, J.; Divekar, P. V.; de Souza, N. J.; Berscheid, H. G.; Fehlhaber, H. W.: Tetrahedron Lett. 983 (1974)
13 Turos, E.; Audia, J. E.; Danishefsky, S. J.: J.Am. Chem. Soc. **111**, 8231 (1989)
14 Rosen, T.; Fernandes, P. B.; Marovich, M. A.; Shen, L.; Mao, J. ; Pernet, A. G.: J. Med. Chem. **32**, 1062 (1989)
15 Brill, G. M.; McAlpine, J. B.; Whittern, D.: J. Antibiot. **41**, 36 (1988); C.A. **108**, 183342d (1988)
16 Ley, S. V.; Smith, S. C.; Woodward, P. R.: Tetrahedron **48**, 1145 (1992)
17 Harris, S. A.; Fisher, L. V.; Folkers, K.: J. Med. Chem. **8**, 478 (1965)
18 Gitterman, C. O.: J. Med. Chem. **8**, 483 (1965)
19 Yuki, H.; Kariya, K.; Hashimoto, Y.: Chem. Pharm. Bull. **15**, 727 (1967)
20 Soliman, F. S. G.: Pharmazie **32**, 572 (1977)
21 Conte, J. E.; Barriere, S. L.: "Manual of antibiotics and infectious diseases", 1st ed., Lea and Febiger, USA, p. 135 (1988)
22 Weislow, O. S.; Kiser, R.; Fine, D. L.; Bader, J.; Shoemaker, R. H.; Boyd, M. R.: J. Natl. Cancer Inst. **81**, 577 (1989), C.A. **111**, 89651v (1989)
23 Boyd, M. R.: Principles and Practices of Oncology **3** (10), 1 (1989)
24 Kappe, T.: Monatsh. Chem. **98**, 874 (1967)

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